Philippine Consensus Statement on the Use of Ketogenic Diet and Intermittent Fasting Diet on Adults for Weight Reduction

Elmer Jasper B. Llanes, MD,[1] Eddieson M. Gonzales, MD,[2] Don Robspierre Reyes, MD,[3] Maria Julia G. Gubat, MSc Nutr Health, RND,[4] Ma. Eloisa Estipona-Villaraza, MS Clin Nutr, RND,[5] Princess Jereme T. Bautista, RND,[6] Lourdes Ella G. Santos, MD,[7] Nanette Rey, MD,[8] Olive Q. De Guzman-Quizon, MD, MPH,[9] Jim Saret, MSAT, C APT, PES,[10] Toni Saret, CPT, PES,[10] Nemencio A. Nicodemus, Jr., MD,[11] Bien J. Matawaran, MD,[12] Cecilia A. Jimeno, MD[13]

1 Division of Cardiovascular Medicine, Department of Internal Medicine, University of The Philippines – Philippine General Hospital
2 Department of Internal Medicine, Batangas Medical Center
3 Section of Cardiology, Department of Internal Medicine, University of Santo Tomas Hospital
4 Department of Science and Technology – Food and Nutrition Research Institute
5 Our Lady of Lourdes Hospital – Nutrition Support Unit; Nutritionist, Dietician Association of The Philippines, Philippine League Against Epilepsy
6 Dietary Department, University of The Philippines – Philippine General Hospital
7 Section of Hypertension, Department of Internal Medicine, University of The Philippines – Philippine General Hospital
8 Department of Internal Medicine, De La Salle Medical and Health Sciences Institute
9 Clinical Nutrition Management Services and Department of Family and Community Medicine, Manila Doctors Hospital; Philippine Society for Parenteral and Enteral Nutrition
10 Philippine Olympic Committee, High Performance Training Program; The Fit Filipino Movement
11 Department of Biochemistry and Molecular Biology, University of The Philippines – College of Medicine; Division of Endocrinology, Diabetes and Metabolism, University of The Philippines – Philippine General Hospital
12 Department of Biochemistry, Molecular Biology and Nutrition, University of Santo Tomas, Faculty of Medicine and Surgery; Section of Endocrinology, Diabetes and Metabolism, Santo Tomas University Hospital
13 Department of Pharmacology and Toxicology, University of The Philippines College of Medicine, Philippine General Hospital, Division of Endocrinology, Diabetes and Metabolism

Corresponding Author
Elmer Jasper B. Llanes, MD, University of the Philippines – Philippine General Hospital
Email: ebllanes@up.edu.ph

INTRODUCTION

Globally, overweight and obesity prevalence have been steadily rising over the years and reaching epidemic proportions due to urbanization, globalization, changes in dietary habits and a decrease in physical activity brought about by easy access to basic needs.

In 2016, global data from the World Health Organization (WHO) showed that among adults aged 18 years old and older, 39% were overweight and 13% were obese as seen in more than 1.9 billion adults. Obesity has nearly tripled since 1975.[1] In the Philippines, data from the National Nutrition and Health Survey (NNHeS) that started since 1993 showed that prevalence of overweight and obese doubled for the past 20 years from 16.6% in 1993 to 31.1% in 2013.[2] Obesity, if not addressed, is closely linked to the development of hypertension, diabetes and metabolic syndrome which ultimately lead to cardiovascular events and even death at an early age.[3,4]

Fad diets have become common solutions to getting to the ultimate goal of achieving ideal body weight through weight reduction. In recent years, both intermittent fasting (IF) and ketogenic diet (KD) have become increasingly popular dietary trends for Filipinos. Media in all platforms have been instrumental in propagating the popularity, and perception of the effectiveness and safety of these two diet regimens.

KD and IF diets are common topics in public fora and much confusion centers on different versions offered, raising concerns for safety. The aim of this group is to release a community-based expression of consensus statements regarding KD and IF based on available clinical trial evidence.

METHODOLOGY

A group of experts from the various medical societies, nutritionists, dietitians and the lay convened to come up with consensus statements on the burning issues on the

use of KD and IF for weight reduction. The group gathered pieces of evidence from clinical trials and from experiences in their respective fields. The moderators collated, reviewed and summarized all the gathered evidences to come up with proposed statements and presented them to the group for consensus voting. The group adapted the Modified Delphi technique wherein a 75% vote (6 out of 8) was determined to carry out with the statements. During the process, all the experts agreed on all these recommendations.

MECHANISM AND ADVERSE EFFECTS OF INTERMITTENT FASTING DIET (IF)

Human fasting is defined as the abstinence from all or some food or drinks for a set period of time. Intermittent fasting (IF) is an interventional strategy in which individuals are subjected to varying periods of fasting.[5] Sometimes called Intermittent Energy Restriction (IER), this approach to weight loss involves short periods of substantial (>70%) energy restriction (ER) interspersed with normal eating. [6]

Below are the different classifications of IF (*Table 1*).[7,8]

Mechanisms of IF

IF involves eating patterns with little or no energy intake for extended time periods alternating with periods of normal food intake.

Calorie control through IF has been shown to benefit cardiovascular status, weight reduction, insulin sensitivity, diabetes control, cognitive function, and cancer prevention among its many effects in humans in several studies.[9]

IF diet can decrease vascular dysfunction, cardiovascular risk and mortality though activation of stress pathways with anti-inflammatory and anti-apoptotic properties by reducing reactive oxygen species, cytokines and leptin and by increasing adiponectin, adenosine monophosphate activated protein kinases, nuclear factor erythroid 2-related factor (Nrf2) and possibly ghrelin. Also, there is improvement and promotion of cellular autophagy.[9]

Table 1. Description of Different Types of IF

Type of IF	Description
Alternate-day fasting	Alternating feast (ad lib intake) and fast days (≤ 25% of energy needs)
Modified fasting regimens	Allows consumption of 20–25% of energy needs on scheduled fasting days; the basis for the popular 5:2 diet, that involves severe energy restriction for two non-consecutive days per week and ad libitum eating for the other 5 days
Time-restricted fasting	Eating only during certain time periods (i.e., 8 h), then fasting or remaining hours of the day
Periodic Fasting	Fasting for up to 24 h once or twice a week with ad lib intake on the remaining days

Mechanisms mediating the weight loss effect of IF:

1. Decrease in plasma glucose by 30%
2. Decrease in insulin by 50%
3. Significant increase in the extent of lipolysis and fat oxidation
4. Moderate increase in the extent proteolysis and protein oxidation

Adverse Effects of IF

In the meta-analysis of Harris et al in 2018 which included six studies of intermittent fasting ranging from 3-12 months among overweight and obese individuals, no serious adverse events were reported by the authors. However, three of the six studies reported minor physical and psychological effects including: headache, reduced energy levels, feeling cold, constipation, light headedness, halitosis, pre-occupation with food, mood swings and lack of concentration.

Other Adverse Events of IF

- Most physical and psychological adverse events were more commonly observed among normal weight individuals in IF than in obese and overweight individuals.
- Additionally, based on a 2011 study of IER, particularly IF, longer average menstrual cycle length after 6 months on IF were experienced among overweight and obese women.
- It is important to take note that adverse events of IF in the long term have not been studied and established.

CONSENSUS STATEMENTS ON THE USE OF IF FOR WEIGHT REDUCTION

1. Overweight or Obese Adults without established ASCVD

For obese adults without established ASCVD, IF, particularly alternate day fasting and modified fasting regimens may be used as a weight loss strategy for 6-12 months.

Most of the studies are on alternate day fasting and modified fasting regimens with very few studies on time restricted feeding and periodic fasting diet.

Summary of Evidence

This statement is based on a meta-analysis of overweight or obese individuals using IF diet compared to continuous energy restriction (CER) or no restriction for weight reduction. It included mostly randomized controlled trials (RCTs) involving 400 participants with duration of these studies ranging from 3-12 months. There were varied methods of the IF across the studies which included alternate day fasting, fasting for 2 days, and up to 4 days per week. CER was defined as energy restriction of 25 to 30% of daily energy requirements while no restriction simply means ad libitum energy intake.[10]

IF was more effective for weight reduction, achieving an average weight loss of 4.1 kgs (-6.3 kgs to 1.99 kg; $p < 0.001$). However, there was no difference comparing

IF to CER in weight reduction (-1.03 kg; 95% CI -2.46 kg to 0.40 kg; *p=0.156*), with both interventions achieving weight loss of approximately 7kgs.[10]

Other cardiovascular risk factors were also measured such as total cholesterol, triglyceride, LDL-cholesterol and blood pressure. A non-significant reduction of these secondary outcomes in IF compared to CER and no calorie restriction was noted.[10]

Another systematic review showed that the degree and rate of weight loss is proportional to the number of fast days per week and the amount energy restriction among those taking the IF diet. Percentage of weight loss is also commensurate to percentage of visceral fat loss.[11] Visceral fat is closely linked to the development of metabolic syndrome, diabetes and possibly cardiovascular disease which makes it an important outcome.[12] IF also improves insulin sensitivity and responsiveness which could therefore decrease the risk of development of diabetes mellitus. [11]

2. Adults with Type 2 Diabetes Mellitus

For adults with T2DM, there are few RCTs and observational clinical outcome studies supporting the existence of a health benefit from IF on weight reduction. Further research in humans is needed before its use can be recommended.

For adults with T2DM, IF is not recommended for weight reduction.

For patients using insulin or insulin secretagogues (SU or Glinides), IF is not recommended due to the risk of hypoglycemia.

For adults with diabetes mellitus on insulin or insulin secretagogues, IF is not recommended for weight reduction.

Summary of Evidence

There are few small studies that support this statement. A two-week observational study involving 10 obese diabetic participants showed that IF can significantly decrease weight by 1.4 kgs and improves fasting glucose and postprandial variability.[13] A pilot trial involving 63 adult diabetics who were overweight or obese with no previous ASCVD were randomized to IF (two days of severe energy restriction (400 to 598 calories/ day) and five days of ad libitum diet) or moderate CER (seven-day continuous energy restriction of 1195 – 1554 calories/day). After 12 weeks, both diets showed a similar but significant reduction of both Hba1c (-0.7 ± 0.9%; p<0.001) and weight (99 ± 14kg to 93 ± 13kg; p<0.001).[14]

However, another RCT involving a smaller population showed a two-fold increase of hypoglycemia during fasting days in those who were on a 5:2 IF diet despite adjustment of doses of insulin and sulfonylureas.[15]

3. Adults who are overweight or obese with established ASCVD

For individuals with a history of ASCVD, no clinical controlled trials exist to support the use of IF for weight reduction. Further research in humans is needed before its use can be recommended.

For obese and overweight adults with established atherosclerotic cardiovascular disease, IF is not recommended for weight reduction.

Summary of Evidence

There is no available evidence for this population.

MECHANISM AND ADVERSE EFFECTS OF KETOGENIC DIET (KD)

KD is defined by a low carbohydrate and high fat content diet. It was first used by Dr. Russel Wilder from the Mayo clinic for treatment of epilepsy in 1921 with weight loss an observed side effect. Sources of fats used for this diet are depicted in the table below.

Types of KD

1. Classical KD is defined as <130 g carbohydrate per day or less than 26% of caloric intake by the American Diabetes Association based on the 2000 kcal/day diet.

2. Very low-carbohydrate ketogenic diet (VLCKD) is composed of 20–50 g/d of carbohydrate or less than 10% of the 2000 kcal/d diet, whether or not ketosis occurs.

Sources of fats on the KD

Patients on the KD for the treatment of epilepsy can have food sources of fats included in the list below. However, this is based on the computed diet by a Registered Dietitian.

Emphasis is mainly focused on the unsaturated fats, while food that are high in saturated fats are proportionately included in the meat plan such as animal meat (Table 2).

Mechanisms and Effects of KD

Ketogenesis starts when there is a decrease in the source of energy from carbohydrates and glucose and there is an increase in the concentration of Acetyl CoA due to increased beta oxidation and gluconeogenesis. The primary role of ketogenesis is to produce a source of energy for the metabolic processes of the body despite the decrease in supply of glucose. This process happens in the liver and is regulated by several mechanisms involving insulin and glucagon.

Mechanism of KD in Producing Weight Loss

The weight loss effect of KD can be summarized in the following proposed mechanisms:[16]

1) Appetite-suppression effects of higher protein intake and direct appetite-reduction effects of ketosis
   a) There is increased feeling of satiety after eating food with higher protein content.
   b) Another mechanism is the direct appetite reduction effect of higher concentration of ketone bodies and its ability to modify levels of some hormones such as ghrelin and leptin. The increase in ghrelin (an appetite-enhancing hormone) that accompanies dietary weight reduction was mitigated when weight-reduced individuals were ketotic.[17]

2) Reduction in lipogenesis and increased lipolysis
   a) This is mediated by the reduction in insulin and increase in glucagon.

3) Greater metabolic efficiency in consuming fats highlighted by the reduction in the resting respiratory quotient (RQ)
   a) RQ indicates which macronutrient is being metabolized (RQ can be used as an indicator of over or underfeeding). Underfeeding, which forces the body to utilize fat stores, will lower the respiratory quotient while overfeeding, which causes lipogenesis, will increase it. Underfeeding is marked by a respiratory quotient below 0.85, while a respiratory quotient greater than 1.0 indicates overfeeding.)
   b) RQ of 0.7 means that fats or lipids are more metabolized.

4) Increased metabolic costs of gluconeogenesis and the thermic effect of proteins
   a) The use of energy from proteins in very low-calorie ketogenic diet (VLCKD) is an expensive process and can lead to a waste of calories, and therefore, increased weight loss.
   b) The energy cost of gluconeogenesis has been confirmed in several studies and it has been calculated at 400–600 Kcal/day (due to both endogenous and food source proteins)
5) Diuretic Effect wherein most of the initial pounds lost are from water weight.

Adverse Effects of KD

Minor adverse effects are commonly reported in studies of ketogenic diets for weight loss. They are classified as short-term adverse effects: constipation, headache, halitosis, muscle cramps, diarrhea, general weakness and rash and long-term adverse effects: disruptions in lipid metabolism, severe hepatic steatosis, hypoproteinemia, mineral deficiencies, increase redox balance, cardiomyopathy and nephrolithiasis.

CONSENSUS STATEMENTS ON THE USE OF KD FOR WEIGHT REDUCTION

1. Overweight or Obese Adults without established ASCVD

For obese adults without established ASCVD, ketogenic diet for 12-24 months has been shown to be associated with weight reduction.

Currently, there is not enough evidence on the effect of KD on normal weight and overweight individuals on weight reduction.

Summary of Evidence

A meta-analysis of 13 randomized controlled trials involving adult obese individuals assigned to low fat diet (i.e., restricted energy diet with <30% of energy of fat) or very low carbohydrate ketogenic diets (i.e., a diet with no more than 50 g carbohydrates/d or 10 % of daily energy from carbohydrates) for a period of 12 months or more showed a significantly greater weight loss among those in the KD group \by almost 1 kg (95% CI – 1.65, - 0.17 kg), p= 0.02, I^2 – 0%, p for heterogeneity = 0.47). There were significant decreases in triglycerides, LDL-C and diastolic blood pressure while HDL-C significantly increased.[18]

Due to the issue of adherence to diet in trials, a small study of 17 male volunteers with BMI between 25 to 35 kg/m^2 was carried out under close supervision. Volunteers were confined to a metabolic ward for a period of four weeks. KD showed weight loss of 2.2 – 0.3 kg for 28 days mostly attributed to body water loss. Loss of total body fat was only 0.5 – 0.2 kgs.[19] The longest study involving morbidly obese adults showed a significant weight loss of 12 kgs coupled by a significant decrease in triglycerides, LDL-C and fasting blood glucose with an increase of HDL-C with no reported adverse events in subjects after 24 weeks on KD.[20]

2. Adults with Type 2 Diabetes Mellitus

For adults with T2DM, there are few small RCTs and observational clinical outcome studies supporting the existence of a health benefit from KD on weight reduction. Further research in humans is needed before its use can be recommended.

For adults with diabetes mellitus, KD is not recommended for weight reduction.

For patients using insulin or insulin secretagogues (SU or Glinides), KD is not recommended due to the risk of hypoglycemia.

Table 2. List of Sources of Fats for KD

SATURATED FATS (From animal food sources)	UNSATURATED FATS (From vegetable food sources)

• All animal meat
• Suet (found in kidneys and loins of beef, sheep and other animals)
• Lard (pig fat)
• Beef Tallow
• Butter, cheese
• Chocolate, cocoa butter
• Coconut oil, Palm oil
• Cream
• Hydrogenated oils
• Stick margarine
• Shortening
• Whole milk
	• Monounsaturated Fats
	  ○ Avocado
	  ○ Canola oil, olive oil, peanut oil
	  ○ Cashew, peanuts, pistachio, hazel nut
	  ○ Olives
	  ○ Peanut butter
	  ○ Non-hydrogenated margarine
	  ○ Poultry
	• Polyunsaturated Fats
	  ○ Almonds, pecans, walnuts
	  ○ Flaxseed, pine nuts
	  ○ corn oil, cottonseed oil, safflower oil
	  ○ soft margarine, mayonnaise
	• Omega-3 Fat
	  ○ Ocean fish (salmon, mackerel, tuna, herring)
	  ○ Shellfish
	  ○ Soy foods
	  ○ Walnuts
	  ○ Wheat germ
	  ○ Some vegetables (spinach, broccoli, lettuce)
	• Trans Fats
	  ○ Margarine (hard stick)
	  ○ Cake, cookies, doughnuts, crackers, chips
	  ○ Meat and dairy products
	  ○ Hydrogenated peanut butter shortening

For adults with diabetes mellitus on insulin or insulin secretagogues, KD is not recommended for weight reduction.

For patients using SGLT2-inhibitors, KD is not recommended due to the added risk of diabetic ketoacidosis.

For patients on SGLT2-inhibitors, KD is not recommended for weight reduction.

Summary of Evidence

Multiple cohort studies comparing KD with other diet regimens (i.e., plate method diet, low calorie diet, moderate-carbohydrate, calorie restricted low fat diet) in overweight and obese adult individuals with T2DM showed that those on KD had more significant weight loss and greater HbA1c reduction. These trials range from four month to 32 months in duration. More weight loss was seen the longer the duration of the KD.[21,22,23]

There were few reported adverse events on the first two weeks on KD which were asthenia, headache, nausea and vomiting; while a few reported constipation and orthostatic hypotension after four months. [23]

Effect on lipid profile of KD compared to low calorie diet showed a significant decrease of total cholesterol, triglycerides and LDL-C while HDL-C significantly increased in favor of KD.[24]

In another study, a significant increase in the LDL-C after one year of nutritional ketosis was noted. Further investigation of the other biomarkers showed an increase in LDL particle size and a decrease in hsCRP and small LDL particles which are the atherogenic particles which cause disease.[25]

An open-label, non-randomized study that included obese diabetic individuals showed that after one year of nutritional ketosis (mostly of omega-3 and omega-6 polyunsaturated fatty acid) using a continuous care intervention showed no increase in incidence of metabolic acidosis but with a mean increase in blood urea nitrogen possibly due to an increase in dietary protein. There were no significant hypoglycemic events reported probably due to close monitoring by their doctors who were allowed to adjust insulin and sulfonylurea doses accordingly. In addition, no change in liver, kidney and thyroid functions were noted after one year of nutritional ketosis with close monitoring.[26]

One case report describes development of euglycemic ketoacidosis in a diabetic patient maintained on SGLT2-inhibitors when low carbohydrate diet was followed. [27]
It is advised to stop all oral hypoglycemic agents except metformin on the first day of KD. Metformin maybe discontinued once blood sugar levels reached <100 mg/dL. Total daily insulin dose should be decreased by 50% at initiation of KD and adjusted accordingly depending on the daily blood glucose levels. [28]

3. Adults who are overweight or obese with ASCVD

For individuals with prior history of ASCVD, there are no clinical controlled trials on KD on weight reduction. However, there are population studies that show long term low-carbohydrate intake is associated with higher mortality. For this high-risk population KD is not recommended.

Summary of Evidence

There is no available evidence for this population.

GENERAL ADVICE FOR WEIGHT LOSS:

1) Lose weight by eating well-balanced diet in appropriate amounts proportionate to your needs and at physiologic intervals coupled with regular and appropriate physical activity.
2) Consult your physician and registered nutritionist-dietitian before engaging in any weight loss diet regimen.

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